

CLAIMS

1. A method of preparing a substituted tetracycline compound, comprising contacting a reactive tetracycline chemical complex comprising a reactive tetracycline-based precursor compound and a transition metal catalyst forming a reactive chemical intermediate with a reactive organic substituent precursor under conditions such that a tetracycline compound substituted with said organic substituent is formed.

5 2. A method of preparing a substituted tetracycline compound, comprising combining a reactive tetracycline-based precursor compound and a reactive organic substituent precursor in the presence of a transition metal catalyst under conditions such that a tetracycline compound substituted with said organic substituent is formed.

10 3. The method of claim 1 or 2, wherein said catalyst comprises an organopalladium catalyst.

15 4. The method of claim 1 or 2, wherein said reactive tetracycline-based precursor compound is a oxytetracycline diazonium salt, iodo derivatized oxytetracycline, boronic acid derivatized oxytetracycline, chlortetetracycline diazonium salt, iodo derivatized chlortetracycline, boronic acid derivatized chlortetracycline, demeclocycline diazonium salt, iodo derivatized demeclocycline, or boronic acid derivatized demeclocycline.

20 5. The method of claim 1 or 2, wherein said reactive tetracycline-based precursor compound is a reactive minocycline-based precursor compound.

25 6. The method of claim 1 or 2, wherein said reactive organic substituent precursor has at least one reactive π -bond containing group.

30 7. The method of claim 1 or 2, wherein said reactive organic substituent precursor is selected from the group consisting of alkenes, substituted alkenes, vinyl monomers, aromatics and heteroaromatics.

35 8. The method of claim 1 or 2, wherein said reactive organic substituent precursor is selected from the group consisting of methylene compounds, aryl boronic acids, active aromatic rings, unsubstituted olefins, substituted olefins, acetylenes, substituted acetylenes, arylethylenes, styrenes, conjugated dienes, isoprenes, vinyl ethers, α , β -unsaturated aldehydes, α , β -unsaturated ketones, aryl vinyl ketones, arylisoprenyl ketones, iodoalkenes, iodoarenes, quinones, α , β -unsaturated acids and their derivatives.

9. The method of claim 3, wherein said catalyst is palladium chloride, palladium acetate, $\text{Pd}(\text{PPh}_3)_4$, $\text{Pd}(\text{AsPh}_3)_4$, $\text{PdCl}_2(\text{PhCN})_2$, $\text{PdCl}_2(\text{Ph}_3\text{P})_2$, $\text{Pd}_2(\text{dba})_3\text{-CHCl}_3$ or combinations thereof.

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10. The method of claim 1 or 2, wherein said catalyst comprises copper.

11. The method of claim 10, wherein said catalyst comprises CuCl_2 , copper (I) triflate, copper thiophene chloride, or combinations thereof.

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12. The method of claim 1 or 2, wherein said catalyst comprises rhodium, iron, iridium, chromium, zirconium, or nickel.

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13. The method of claim 12, wherein said catalyst comprises rhodium (II) acetate or $\text{Rh}_6(\text{CO})_{16}$.

14. The method of claim 5, wherein said reactive minocycline-based precursor compound is a minocycline diazonium salt, iodo derivatized minocycline, or boronic acid derivatized minocycline.

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15. The method of claim 1 or 2, wherein said reactive tetracycline-based precursor compound is a reactive doxycycline-based precursor compound.

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16. The method of claim 15, wherein said reactive doxycycline-based precursor compound is a doxycycline diazonium salt, iodo derivatized doxycycline, or boronic acid derivatized doxycycline.

17. The method of claim 1 or 2, wherein said reactive tetracycline-based precursor compound is a reactive sencycline-based precursor compound.

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18. The method of claim 17, wherein said reactive sencycline-based precursor compound is a sencycline diazonium salt, iodo derivatized sencycline, or boronic acid derivatized sencycline.

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19. The method of claim 1 or 2, wherein said reactive tetracycline-based precursor compound is a tetracycline diazonium salt, iodo derivatized tetracycline, or boronic acid derivatized tetracycline.

20. The method of claim 1 or 2, wherein said reactive tetracycline-based precursor compound is a chelocardin diazonium salt, iodo derivatized chelocardin, boronic acid derivatized chelocardin, rolitetracycline diazonium salt, iodo derivatized rolitetracycline, boronic acid derivatized rolitetracycline, lymecycline diazonium salt, iodo derivatized lymecycline, or boronic acid derivatized lymecycline.

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21. The method of claim 1 or 2, wherein said reactive tetracycline-based precursor compound is a methacycline diazonium salt, iodo derivatized methacycline, boronic acid derivatized methacycline, apicycline diazonium salt, iodo derivatized apicycline, boronic acid derivatized apicycline, clomocycline diazonium salt, iodo derivatized clomocycline, or boronic acid derivatized clomocycline.

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22. The method of claim 1 or 2, wherein said reactive tetracycline-based precursor compound is a methacycline diazonium salt, iodo derivatized methacycline, boronic acid derivatized methacycline, apicycline diazonium salt, iodo derivatized apicycline, boronic acid derivatized apicycline, clomocycline diazonium salt, iodo derivatized clomocycline, or boronic acid derivatized clomocycline.

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23. The method of claim 1 or 2, wherein said reactive tetracycline-based precursor compound is a guamecycline diazonium salt, iodo derivatized guamecycline, boronic acid derivatized guamecycline, meglucycline diazonium salt, iodo derivatized meglucycline, boronic acid derivatized meglucycline, mepylcycline diazonium salt, iodo derivatized mepylcycline, or boronic acid derivatized mepylcycline.

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24. The method of claim 1 or 2, wherein said reactive tetracycline-based precursor compound is a penimepicycline diazonium salt, iodo derivatized penimepicycline, boronic acid derivatized penimepicycline, pipacycline diazonium salt, iodo derivatized pipacycline, boronic acid derivatized pipacycline, etamocycline diazonium salt, iodo derivatized etamocycline, boronic acid derivatized etamocycline, penimocycline diazonium salt, iodo derivatized penimocycline, or boronic acid derivatized penimocycline.

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25. A method of preparing a doxycycline compound substituted with an aryl substituent, comprising combining a reactive doxycycline-based precursor compound and an aryl boronic acid in the presence of a transition metal catalyst under conditions such that a doxycycline compound substituted with an aryl substituent is formed.

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26. The method of claim 25, wherein said reactive doxycycline-based precursor compound is 9-diazonium doxycycline.

27. The method of claim 25, wherein said catalyst is an organopalladium catalyst.
28. The method of claim 27, wherein said organopalladium catalyst is palladium acetate.